Decision Memo for Autologous Stem Cell Transplantation for AL Amyloidosis (CAG-00050N)

Decision Summary

HCFA conducted a thorough review of the request submitted by the Boston Medical Center and has concluded that a sufficient body of evidence does not exist to justify a national coverage decision in favor of AuSCT for patients with AL amyloidosis. A substantial portion of the submitted materials did not meet the criteria for consideration described above. Analysis of these studies identifies important biases that were not addressed. Small sample sizes and discriminatory enrollment of patients introduces selection bias, which can lead to skewed results. Furthermore, none of these studies compare HDCT and AuSCT to either a control group or other treatment modalities. It is difficult to determine the effectiveness of a treatment unless it is compared to current standards of care. Safety is another concern that was identified. The wide range in treatment-related mortality (0, 12%, and 43%) leads to the conclusion that proper patient selection may be an issue.

Moreover, there is little indication that AuSCT has become the standard of care in treating AL amyloidosis. The utilization of this procedure in the United States appears to be highly localized to specialized medical centers. It is apparent by the evidence that much of the research conducted on this topic is relatively preliminary, perhaps no more than five years old. Leading researchers in the field differ on the safety and efficacy of the procedure. Kyle 1999, states that "confirmation of the favorable results obtained from AuSCT for primary AL is necessary... Consequently, a cohort of patients with primary AL who are eligible for transplant must be randomized to receive the best available chemotherapy regimen or AuSCT". The author also identifies a need for long-term follow-up studies before conclusive determinations on safety and efficacy can be made.

We note that none of the three cited studies involved any patients over 63. This procedure may in fact carry greater risk with advanced age; age has been suggested as a prognostic factor. In addition, the studies cited above were limited to AL amyloidosis. AuSCT in senile, familial, and slower forms of the disease has *not* been considered in this review. Since there is no evidence relating to the safety and efficacy of AuSCT for treatment of non-primary amyloidosis, or for treatment of any type of amyloidosis in patients over age 63, we believe it is appropriate to issue a national coverage policy that would exclude coverage of AuSCT for these situations. Further, the evidence on AuSCT for AL amyloidosis in younger patients (less than 64) is insufficient to change current Medicare coverage policy. Medicare beneficiaries, at this time, are best served if HCFA maintains its policy of contractor discretion in these situations.

HCFA is willing to reconsider this coverage determination if new evidence becomes available. If this issue is revisited, HCFA would especially be interested in seeing prospective randomized clinical trials that compare AuSCT to standard chemotherapy with larger, more diverse sample sizes that address the Medicare population.

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Decision Memo

To: File: Autologous Stem Cell Transplantation for AL Amyloidosis
CAG-00050N

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Re: National Coverage Policy Request

Date: January 14, 2000

This memorandum serves four purposes: (1) describes the etiology of primary (AL) amyloidosis and treatments currently available; (2) outlines current coverage policy for autologous stem cell transplantation (AuSCT); (3) analyzes relevant clinical literature; and (4) delineates reasons for limiting Medicare's current policy of contractor discretion.

Description and Background of AL Amyloidosis

AL amyloidosis is a hematological disorder, associated with plasma cell dyscrasias, in which extra-cellular insoluble protein (amyloid) fibrils accumulate in various tissues and organs throughout the body. These amyloid fibrils, formed by monoclonal populations of plasma cells in the bone marrow, consist of abnormal variable portions of immunoglobulin (Ig) light chain proteins (M proteins). Except for those within the central nervous system, amyloid fibrils can affect any major organ in the body. The most common organs affected are the kidney, heart, liver, and autonomic or peripheral nerves.

AL amyloidosis is a rare disease; only 1200 to 3200 new cases are reported each year in the United States.[1] It is similar in many ways to multiple myeloma, another plasma cell dyscrasia. In multiple myeloma, plasma cells proliferate and accumulate in the patient's bone marrow, replacing healthy tissue, and produce M-proteins. Two thirds of patients with AL amyloidosis are male and less then 5% of patients are under 40 years of age.[2] Both the etiology of AL amyloidosis and the mechanism of amyloid deposition remain poorly understood.

The clinical course of AL amyloidosis is usually associated with rapid disease progression, involvement of multiple organ systems, and short survival periods. Extensive organ system impairment, secondary to amyloid deposits, often results in death. Due to the rapid progression of AL amyloidosis, median survival from diagnosis is between one to two years, depending on which organ systems are affected. Patients with cardiac amyloid involvement have an even poorer prognosis with a median survival of less than six months, thus accounting for almost one half of deaths from AL amyloidosis.[3] Due to its similarities to multiple myeloma, treatment of AL amyloidosis has largely been focused around oral chemotherapy regimens. Patients are treated with standard doses of drugs such as melphalan, prednisone, and/or colchicine. Research suggests that multiple drug regimens can produce better response rates then single drug regimens.[4] However, response rates to standard chemotherapy are quite low. For example, many patients do not live long enough to receive enough cycles of melphalan to actually benefit from treatment.

On September 17, 1999, the Health Care Financing Administration (HCFA) received a formal request from the Boston Medical Center for the coverage of AuSCT in the treatment of AL amyloidosis. Evidence is cautiously emerging that suggests a clinical benefit of using AuSCT (described below) in conjunction with high-dose chemotherapy (HDCT) regimens to slow the progression of the disease in patients. Therefore, HCFA must evaluate whether enough substantive scientific evidence has accumulated to justify a national coverage decision.

Description and Current Coverage Policy for Stem Cell Transplantation

Stem cell transplantation is defined as a process in which stem cells, immature cells from which all blood cells develop, are harvested from either a patient's or donor's bone marrow or peripheral blood for intravenous infusion. The stem cells are treated with drugs to eradicate existing cancer cells and then frozen until transplanted into a recipient.[5] The transplant can be used to effect hematopoietic reconstitution following severely high doses of chemotherapy and/or radiotherapy. There are two main types of bone marrow transplantation: allogeneic and autologous. Allogeneic stem cell transplantation is a procedure in which stem cells or bone marrow is obtained from a healthy donor. AuSCT restores stem cells using the patient's own previously harvested cells.

The *Coverage Issues Manual* (*CIM*) addresses Medicare's coverage policy for stem cell transplantation in §35-30.1. National coverage determinations for allogeneic stem cell transplantation have been made for treatment of the following conditions, after careful review and conclusion that such treatments are both reasonable and necessary:

- leukemia
- leukemia in remission
- aplastic anemia
- severe combined immunodeficiency disease
- Wiskott-Aldrich syndrome.

Medicare does not cover allogeneic stem cell transplantation for the treatment of multiple myeloma.

National coverage determinations for AuSCT have been made for treatment of the following conditions, after careful review and conclusion that such treatments are both reasonable and necessary:

- acute leukemia in remission with a high probability of relapse and having no human leukocyte antigens (HLA)-matched donor
- resistant non-Hodgkin's lymphomas or presenting with poor prognostic features following an initial response
- recurrent or refractory neuroblastoma,
- advanced Hodgkin's disease upon failing conventional therapy and having no HLA-matched donor

Medicare does not cover AuSCT for the treatment of the following conditions:

- acute leukemia not in remission
- chronic granulocytic leukemia
- solid tumors (other than neuroblastoma)

- multiple myeloma

In the absence of specific written coverage policies on other conditions in which stem cell transplantation may be used, Medicare contractors have the authority to develop local medical review policies (LMRPs). In developing local policies, assisted by their Contractor Advisory Committees (CAC), contractors must determine that the service is reasonable and necessary. LMRPs may vary from one state to another and may include instructions limiting the service and/or identifying clinical indications for its use.

Analysis of Clinical Evidence

The analysis established in this memorandum is limited to AuSCT for the treatment of AL amyloidosis. A coverage determination for allogeneic stem cell transplantation was not requested.

In its deliberation on this formal request, HCFA considered twenty-three distinct pieces of scientific material. In order to focus analysis on literature that only presents *direct* evidence on AuSCT on patients with AL amyloidosis, the following were excluded:

- Individual case studies
- Abstracts
- Overview article providing only background information on AL amyloidosis
- Clinical evidence that does not focus on AuSCT

This memorandum will review the following three studies that were not subject to exclusion:

- In Comenzo *et al.* 1996, five AL amyloidosis patients (median age of 41, range 18-61) were treated with dose-intensive intravenous (IV) melphalan followed by AuSCT. At 13 months, all five patients demonstrated either improvements in amyloid-related organ dysfunction and performance status or showed disease stability. After 12 months, plasma cell dyscrasias could not be detected in three patients. It was concluded that AuSCT could be conducted safely with dramatic improvements in outcome on patients with AL amyloidosis.
- In Comenzo *et al*. 1998 (a continuance of the previous study), 25 patients (median age 48, range 29-60) with proven AL amyloidosis were enrolled in a phase-II clinical study to receive dose-intensive IV melphalan followed by AuSCT. At 24 months, 68% of the patients were alive. Of this group, 87% of patients with two or less major organ systems involved had survived compared to only 40% of patients with greater than two involved systems. Furthermore, only 38% of patients with predominant cardiac involvement had survived compared to 82% of patients without cardiac involvement. At three months post transplant, 62% of surviving patients had achieved complete response of their clonal plasma cell disorder. Three patients (12%) died within 100 days of transplantation. The authors suggests that patients with predominant cardiac involvement, particularly those with more than 2 involved organ systems, are high-risk candidates for AuSCT.
- In Moreau *et al*. 1998, 21 patients (median age 48, range 36-62) with confirmed AL amyloidosis underwent AuSCT with high-dose melphalan. Patients with secondary, familial, senile, localized amyloidosis or overt symptomatic multiple myeloma were not included in this study. Authors noted that the number of patients who could not proceed to AuSCT was unknown. There were 9 toxicity-related deaths observed within the first month (a treatment mortality rate of 43%). At 14 months, 10 of the 12 surviving patients (83%) experienced response to treatment with improved organ function (representing 47% of all patients). Actuarial 4-year event free survival was 29.9% for the entire study. The number of clinical manifestations is identified as a possible prognostic factor.

All three studies contain extremely small sample sizes. In addition, there is almost no description on how patients were enrolled into the study. No comparisons are made to either a control group or alternative mode of treatment in any of the three studies. Because of these design issues, it is difficult to assess the significance of the results produced by the three studies. Serious safety concerns are also raised by Moreau *et al* because of the high toxicity rate associated with AuSCT. Furthermore, the authors' lack of specified exclusion criteria and the inability to account for AuSCT-intolerant patients points to potential selection bias within the data.

For a complete review of all scientific material submitted by the Boston Medical Center and HCFA, please refer to the literature review and bibliography attached to this memorandum.

Coverage Decision

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[1] Falk R, Comenzo R, et al.

[2] Hussein M.

[3] Hussein M

[4] Skinner M, Anderson J, et al.

[5] National Cancer Institute/PDQ Glossary found at cancer.med.upenn.edu/pdq_html/glossary/psct.html

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Literature Review

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